Galactose and Fructose

Introduction

Glucose comes into our bodies through our diet. Glucose is a simple sugar. There are commonly ingested complex sugars that result in glycolysis. These complex sugars may contain glucose. But they may contain other sugars as well. There were two evolutionary options for managing this option for multiple simple sugars: develop completely separate pathways per sugar, or somehow find a way to get other sugars into our common pathway. We opted evolutionarily to combine them. This lesson will discuss fructose and galactose metabolism and diseases that arise from enzyme deficiencies.

Galactose Metabolism

Lactose is a complex sugar that comes from dairy. **Lactose** is broken down in the gut by **lactase** into glucose and galactose. Glucose we know how to handle. Galactose enters the blood through the intestinal lumen without issue. Its first stop is the liver, receiving all of the blood from the portal circulation (this becomes relevant in deficiency, below). Normally what happens is galactose gets into cells and **gets trapped by phosphorylation**. In much the same way hexokinase did the trapping in the cell for glucose, **galactokinase** (the kinase-enzyme for galactose) phosphorylates galactose. It's a high-energy bond and requires ATP, just like glucose. **Galactose-1-phosphate** then undergoes a compositional change caused by **uridylyl transferase**, turning galactose-1-phosphate into **glucose-1-phosphate**. The mechanism is NOT important to know, just that it happens.

Glucose-1-phosphate is the branch-point. Glucose-1-phosphate, as we'll see, can go on to be stored as glycogen, and comes from glucose-6-phosphate. That's to say, the original **galactose**, now turned **glucose-1-phosphate**, can go to glycogen storage. Or, glucose-1-phosphate can become **glucose-6-phosphate** and enter glycolysis as normal. Thus, galactose works just like glucose—sort of. Galactose has a galactokinase instead of a hexokinase, and a uridylyltransferase to get it to be glucose. That one extra step with a hard-to-say name was an extra step, but it also situated galactose at a powerful position—glycolysis or glycogen.

Deficiency with Galactose Metabolism

Galactokinase deficiency. Galactose is like glucose; it freely passes through the membrane through its transporter. It travels down its concentration gradient. And, like glucose, **it must be trapped in the cell by phosphorylation** if it's to remain. Failure to phosphorylate the galactose by galactokinase will result in **none of the galactose entering glycolysis**. On its own, this isn't so bad. The galactose levels get high enough, and they just get urinated out. Like in diabetes (excess glucose), that can lead to dehydration. But what's worse is that **galactose accumulates everywhere**, the blood included, and in the eye. It just so happens that the eye has an enzyme that's designed for something else, called **aldose reductase**. Normally, it doesn't do anything to galactose, because galactose is burned like glucose. But if galactose accumulates, it'll accumulate everywhere; and in the eye, aldose reductase turns galactose into **galactitol**. Galactose wasn't trapped in the cell, but in the form of galactitol, it is trapped. And just as the excess galactose was urinated out, osmotically pulling water with it leading to dehydration, the osmotically active and trapped-in-the-eye galactitol causes osmotic damage. That osmotic swelling causes damage to the lens and produces **cataracts in infancy**.

Aldose reductase has a high K_M (low affinity) for galactose. Only in the pathologic condition where galactose levels rise to supra-normal levels does the aldose reductase start to act on galactose.

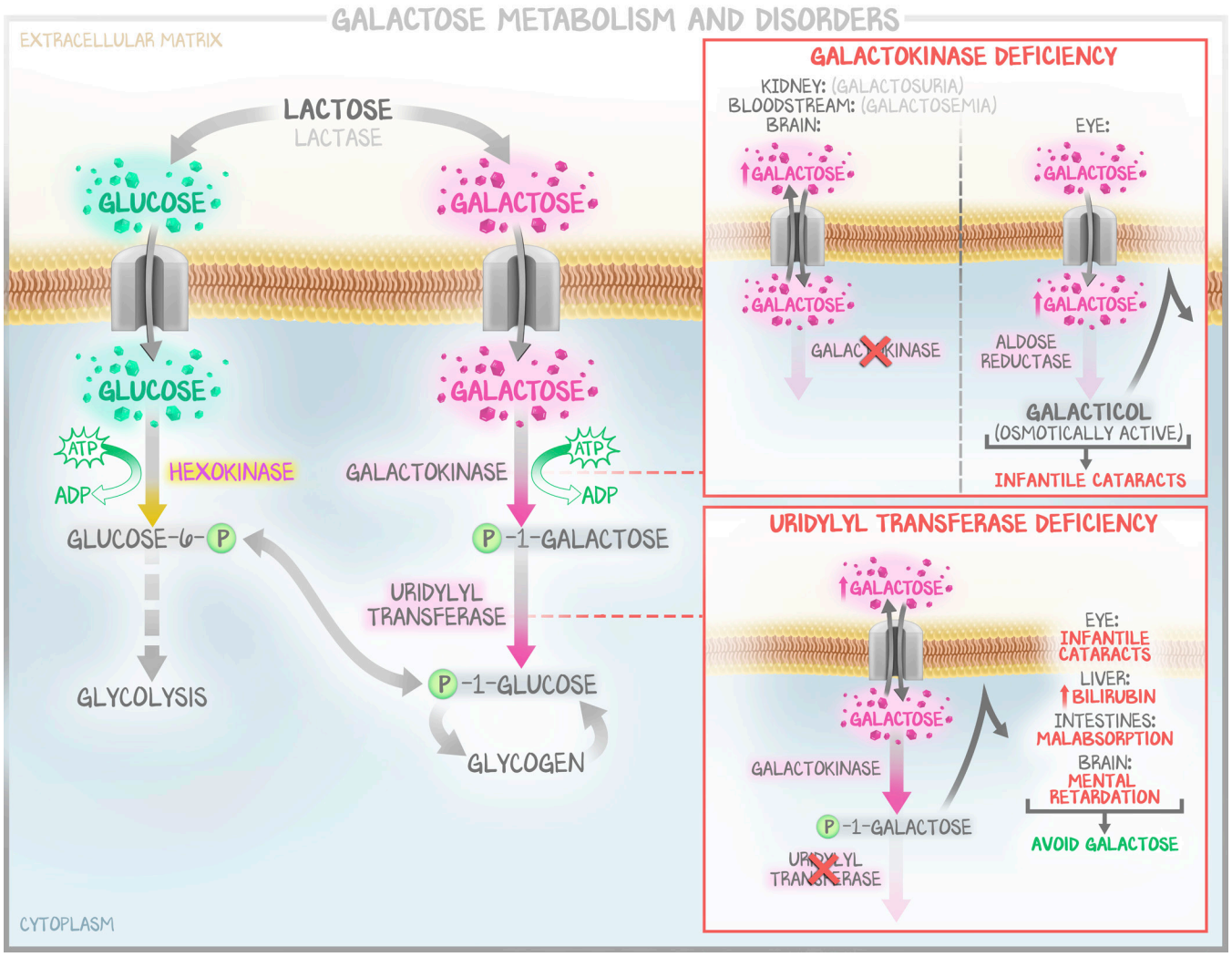

Figure 10.1: Galactose Metabolism and Disorders
Normally, galactose enters gycolysis as glucose-6-phosphate through glucose-1-phosphate. There are two deficiencies. Galactokinase deficiency causes accumulation of galacticol in the eye. Uridylyltransferase deficiency causes accumulation of galactose-1-phosphate in all tissues.

Galactose-1-phosphate uridylyltransferase deficiency. We already spent a bit of time with the story of osmotically active galactose and galactitol, so we don't need to do it again. If galactokinase is intact, galactose gets into cells, and gets trapped there, phosphorylated to galactose-1-phosphate. To get into either the glycogen or the glycolysis pathway, galactose-1-phosphate must be turned into glucose-1-phosphate. If it doesn't . . . there's nothing else for galactose-1-phosphate to do except sit there. An **osmotically active galactose-1-phosphate** is trapped in cells. Permanently. Since the **first cells to see** galactose are the **enterocytes** and **hepatocytes** from portal circulation, the liver gets it the worst. Osmotic damage in the lens causes cataracts, yes. But osmotic damage to the liver causes hyperbilirubinemia. Osmotic damage in the brain leads to mental retardation. Osmotic damage in the gut prevents absorption, causing vomiting and diarrhea. These kids are sick.

The "worse one" is galactose-1-phosphate uridylyltransferase. But **cataracts in infancy** can mean nothing other than **galactose metabolism**. We could avoid the problem by **avoiding lactose**, but often the damage is done and the presentation obvious before the disorder (which is extremely rare) is detected.

Lactase deficiency. An adult disease, which we'll throw in here because it's related to galactose metabolism, is prevalent in **Asians**. With lactase deficiency, lactose can't be broken down into galactose or glucose. Osmotically active, lactose in the gut causes diarrhea. Worse for the patient is the gut bacteria (with their lac operons) that happily consume the lactose, leading to flatulence, foul stool, and diarrhea. While we haven't established the "correct dose," replacing the enzyme in the diet at the time of lactose consumption can avoid the symptoms.

Fructose Metabolism

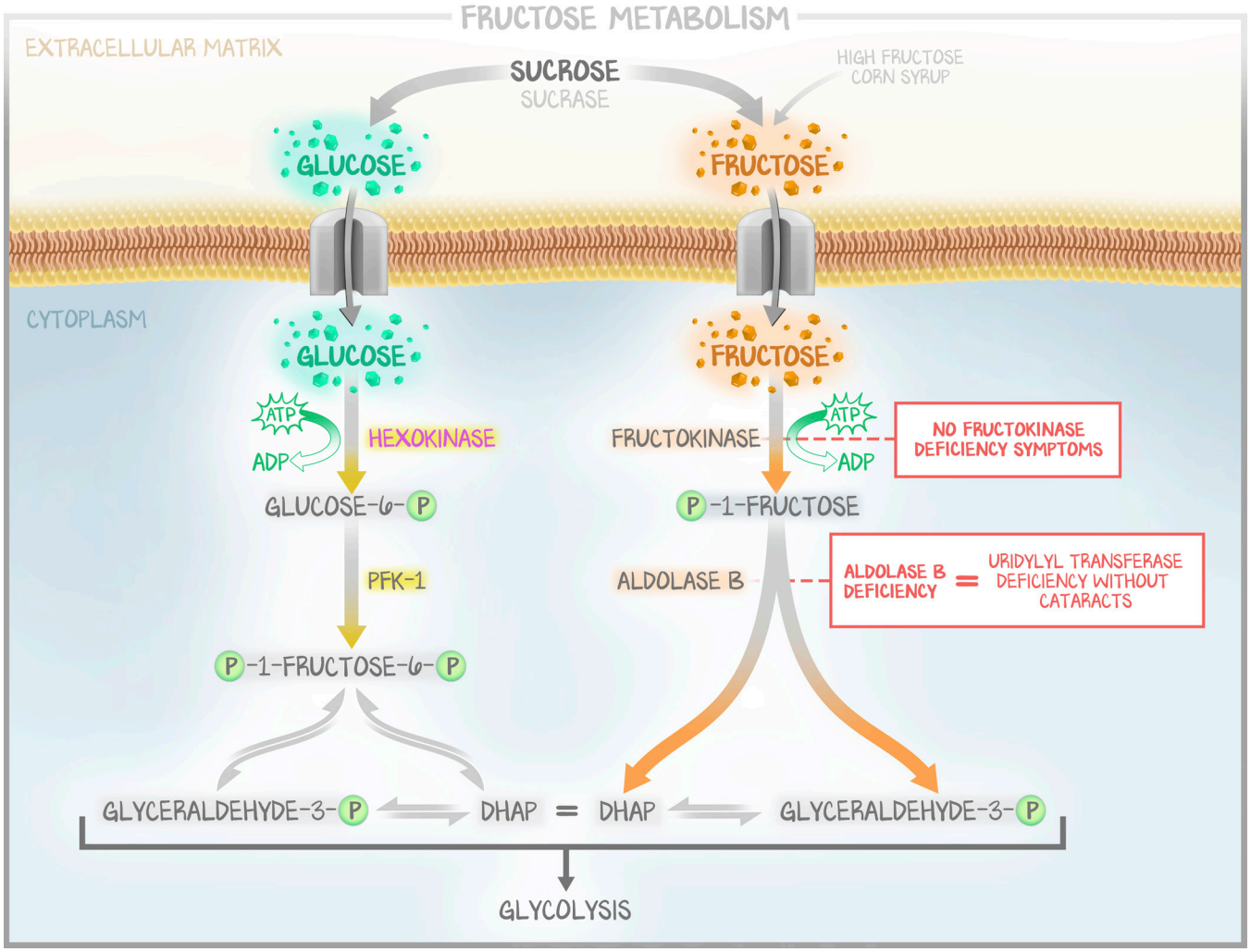

Figure 10.2: Fructose Metabolism
Fructose is converted to glyceraldehyde-3-phosphate to enter glycolysis. Aldolase B deficiency is similar to uridylyltransferase of galactose. Fructokinase deficiency does not have symptoms, as hexokinase can also work on fructose.

Fructose shares many similarities with galactose, but not the deficiency. Sucrose is sweet. It's table syrup, the thing you think of as "sugar" in the pantry. Sucrose is broken down by **sucrase** into glucose and **fructose**. Fructose gets into cells and is quickly trapped in the cell by **fructokinase**. If fructokinase doesn't do it, hexokinase will, but slower, so there's no syndrome that accompanies fructokinase

deficiency. Glucokinase's K_M for fructose is higher (lower affinity) than glucose's, but close enough so that no disorder occurs as fructose levels rise. Trapped as **fructose-1-phosphate** (be careful, we used fructose-6-phosphate in glycolysis), another enzyme named **aldolase B** takes fructose-1-phosphate to DHAP and glyceraldehyde-3-phosphate; the exact same spot after **PFK-1** takes fructose-1-phosphate to DHAP and glyceraldehyde-3-phosphate.

That means that through fructokinase and aldolase B, fructose enters glycolysis as if it were glucose, except that it **escapes the regulatory step of PKF-1**. This has gained the attention of nutritionists. While the caloric quantity of fructose is the same as glucose—it provides the same ATP—it does so by providing a faster burst of energy by supplying the pathway with more substrate. That's great when athletes drink a sweet drink on the sidelines during a game. But what's not is when it's consumed in excess, often and regularly, in the form of high-fructose corn syrup. Accumulation of energy leads to an overfed state, and accumulation of fatty acids. That means fat, increasing obesity. And we're leaving out what fructose doesn't do for satiety and other endocrine mechanisms—just the biochemistry alone is bad.

Aldolase deficiency does the same thing as uridylyltransferase deficiency: osmotic accumulation in the liver causes liver damage, lethargy, and **Fanconi syndrome** rather than cataracts. Cataracts would be an issue (fructose does accumulate) except for the fact that aldose reductase simply cannot use fructose as a substrate.

If infantile cataracts, it's a problem with galactose.

If really sick and systemic, it is either galactose-1-phosphate uridylyltransferase deficiency (galactose, with cataracts) or it's aldolase deficiency (fructose, without cataracts).